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(54) Title: PHARMACEUTICAL COMPOSITION FOR TREATMENT OF SYNAPTIC DYSFUNCTION COMPRISING AN OXIME

(57) Abstract

A pharmaceutical composition is provided for treatment of chronic symptoms of synaptic dysfunction and related disease disorders comprising an effective amount of a pharmaceutically acceptable oxime which is physiologically active such as an acetylcholine esterase reactivator optionally in association with an additional pharmacologically active agent. The pharmaceutical composition has wide-ranging applicability in the treatment of withdrawal symptoms due to the cessation of tobacco use, respiratory disease, drug and alcohol addiction, disorders of the central and peripheral nervous systems, treatment of antineoplastic disease as well as the reduction of adverse effects of antineoplastic disease treatment, cardiac disorders and circulatory disease, obesity, fatigue syndromes, endocrine and immune system disorders, dysfunction of gastrointestinal motility and irritable bowel syndrome, and heavy metal poisoning.

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PHARMACEUTICAL COMPOSITION FOR TREATMENT OF SYNAPTIC DYSFUNCTION COMPRISING AN OXIME

BACKGROUND OF THE PRESENT INVENTION

The pharmaceutical composition of the present invention may be used to treat a variety of chronic symptoms of synaptic dysfunction and related disease disorders in mammals including humans. The composition of the present invention may be used to treat chronic symptoms of synaptic dysfunction and related diseases such as withdrawal symptoms due to the cessation of tobacco use, respiratory disease, drug and alcohol addiction, disorders of the central and peripheral nervous systems, treatment of antineoplastic disease as well as the reduction of adverse effects of antineoplastic disease treatment, obesity, endocrine and immune system disorders, cardiac disorders and circulatory disease, fatigue syndromes, dysfunction of gastrointestinal motility and irritable bowel syndrome and heavy metal poisoning.

Tobacco use is recognized as constituting a significant health hazard. The particular health hazard may vary depending upon whether the tobacco use results from smoking (i.e., cigarette, cigar and pipe smoking) or from a non-smoking activity (i.e., use of smokeless or chewing tobacco). Many of the health hazards associated with the use of tobacco may be alleviated upon cessation of tobacco use. Even if not totally alleviated, many health risks associated with such use may still be reduced.

Many methods have been proposed and/or attempted to assist persons to reduce or cease

tobacco use. See, for example, U.S. Patent Nos. 3,877,468 (chewable tobacco substitute containing tobacco alkaloid); 3,901,248 (chewable tobacco

substitute containing nicotine); 4,255,439 (administration of 2-imidazoline derivative in combination with an anorectic); 4,276,890 (gamma pyrone); 4,555,397 (administration of atropine and scopolamine potentiated with chlorpromazine); 4,596,706 (administration of ethylene trithiocarbonate or colloidal sulfur); 4,800,204 (administration of dopamine receptor agonist); 4,806,356 (nicotine lozenge); 4,832,994 (administration of silver acetate); 4,597,961 (transdermal administration of nicotine); 4,999,382 (administration of serotoninergic drugs); 5,021,457 (administration of phenylpropanolamine); 5,051,426 (administration of serotonin antagonist and CNS stimulant); 5,234,947 (potassium channel activators); 5,362,496 (sequential transdermal and transmucosal administration of nicotine); 5,409,946 (administration of isoxazole, isothiazole and pyrazole compounds); 5,414,005 (administration of lobeline); 5,480,651 (administration of non-specific acetylcholine agonist and a muscarinic agonist); 5,549,906 (lozenge of nicotine, nonnutritive sweetener and an absorbent excipient); 5,574,052 (administration of nicotine receptor activating drug together with antagonist to the nicotine receptor activating drug); 5,592,956 (herbs applied to acupuncture points of body); 5,593,684 (concurrent transdermal and transmucosal administration of nicotine); 5,599,554 (administration of nicotine and caffeine); 5,612,357 (cotinine); 5,662,920 (nicotine lozenge); 5,691,365 (nicotine receptor antagonists); 5,696,115 (benzodiazepine); and WO 91/09599 (administration of inclusion complex of

nicotine and cyclodextrin). Psychiatric counseling has also been employed in an attempt to bolster the person's ability to cease or control tobacco use.

Unfortunately, none of the above methods of treatment have been very successful. While such treatments may bring short-term relief to the person, long-term success has not been easily achieved. The degree of success of such methods is generally not predictable due to the fact that the degree of success achieved is dependent upon the susceptibility of the person to the particular treatment employed. In fact, it is believed that some persons are more susceptible to the effects of tobacco use than others with the result that such persons are not easily or readily able to cease such use by means of conventional treatment methods. This is particularly believed to be the case when tobacco use begins during the teenage years and continues into adulthood. Factors such as extent of tobacco use (frequency) and type of tobacco use (smoking vs. non-smoking tobacco use) play a role in the difficulty encountered by a person upon attempting to cease or reduce the extent of tobacco use. Also, comorbid addictions, stress, psychiatric disorders and environmental factors may exacerbate the difficulty encountered by a particular person in ceasing tobacco use. It is believed, for example, that xenobiotic toxic agents such as pesticides, insecticides, fungicides, oxidants, solvents and other environmental toxins encountered by the person by various means (e.g., via drinking water and/or food impurities, etc.) contribute to the inability of the person to cease or control tobacco use. It

would be desirable to provide a method to assist in tobacco use cessation by alleviating withdrawal symptoms resulting from cessation of tobacco use.

Respiratory diseases are also many in number. For instance, bronchoconstriction associated with pulmonary disease is very prevalant and associated with a number of diseases. These diseases include asthma, chronic obstructive pulmonary disease (COPD), and pulmonary hypersensitivity.

Asthma is a term given to a condition whereby a person experiences wheezing and difficulty in breathing due to the constriction of the air passages in the lungs. It has been believed that this state is due to an allergic reaction of some sort and generally non-defined. It is estimated, for example, that 5 million children in the United States alone suffer from the symptoms of asthma. It has also been reported that 500,000 hospital admissions and 5000 deaths each year may be attributable to asthma. COPD affects more than 15 million persons in the United States. COPD symptoms include chronic cough, shortness of breath and difficulty breathing, and predominates in two forms, chronic bronchitis and emphysema. Additional respiratory diseases such as allergic rhinitis, conjunctivitis, Epiglottis, Laringotrachitis, Urticaria and other allergic and neurodermatitis are often associated with these conditions.

A variety of treatments have been tried to alleviate or control such symptoms. Present asthma treatments involve minimizing contact with allerginic agents as well as use of bronchodilators. However, it is possible that in certain instances the use of a bronchodilator

exacerbates the condition rather than provide any long term relief from the symptoms due to the gaseous delivery system employed. Bronchoconstriction therapy has also included administration of beta-adrenergic agonists, ipratropium and methylxanthines. Treatment of COPD includes administration of ipratropium (Atrovent), albuterol (Proventil, Ventolin) and theophylline. In extreme cases, lung resection and transplantation are recommended.

Exemplary therapies are disclosed in U.S. patent Nos. 1,794,292 (atropine); 3,950,519 (cedar resin); 4,031,218 (xanthines); 4,089,959 (xanthines); 4,120,947 (xanthines); 4,353,922 (anticholinergic bronchodilators); 4,689,213 (calcium channel blocker); 4,816,487 (1-(2-hydroxyaryl)-alkane-1-on-oximes); 5,096,916 and 5,250,286 (imidazoline); 5,124,455 (oxime-carbonate and oxime-carbamate); 5,171,744 and 5,292,749 (antimuscarinic bronchodilator); 5,234,947 (potassium channel activators); 5,362,755 and 5,547,994 (albuterol); 5,409,934 (xanthines); 5,552,407 (methylecgonidine); 5,650,444 (biphenyl oxime derivatives); and 5,693,659 (substituted oxime derivatives).

As a complicating factor in the treatment of respiratory disease and allergies, it is believed that factors such as comorbid addictions, stress, psychiatric disorders and environmental factors play a role in determining the extent to which a particular person may be afflicted by the symptoms of respiratory disease and allergies. For example, xenobiotic agents such as pesticides, insecticides, fungicides, oxidants, solvents and other environmental toxins encountered by the

person by various means (e.g., drinking water, food contaminantion, smoking, etc.) may contribute to the susceptibility of the person to respiratory disease and allergies as well as the severity of symptoms of such diseases.

A need thus exists to provide a method of treatment of respiratory disease and allergies suffered by mammals and in particular humans which enables the root cause of the respiratory disease and/or allergy to be addressed whereby further occurrences of the disease or allergy are avoided or at the least minimized. It may be possible, for example, to avoid the need for surgery which may otherwise be required in an attempt to restore acceptable lung function in cases such as extreme COPD.

Drug and alcohol addiction and/or abuse is extremely common. Addiction is generally defined as a state of periodic or chronic intoxication detrimental to the individual which results from repeated administration of the drug. The addicted individual is subject to significant symptoms of withdrawal upon attempting to cease use of the addictive substance (whether alcohol or drugs such as cocaine, heroine, or conventional painkillers).

A number of medical therapies have been tried with differing success in the treatment of alcohol and drug addiction. See, for example, U.S. patent Nos. 4,786,653; 4,847,281; 4,919,916; 4,935,429; 4,942,182; 4,948,803; 4,956,391; 5,028,611; 5,051,426; 5,059,600; 5,075,341; 5,093,129; 5,102,913; 5,114,942; 5,130,338; 5,180,729; 5,185,329; 5,189,064; 5,223,497; 5,232,934; 5,397,782; 5,462,948; 5,556,837; and 5,703,100.

Unfortunately, none of the above methods of treatment have been very successful. While such treatments may bring short-term relief to the person, long-term success has not been easily achieved. The degree of success of such methods is generally not predictable due to the fact that the degree of success achieved is dependent upon the susceptibility of the person to the particular treatment employed. The potential effect of xenobiotic toxins (such as pesticides, fungicides, solvents, heavy metals, food additives, etc. as well as other environmental contaminants) has not been well-studied in relation to the occurrence and severity of alcohol and drug addiction and/or abuse. However, it would be desirable to provide a method of treatment which assists in overcoming the drug and alcohol addiction.

Disorders of the central and peripheral nervous systems are many in number. Generally included within any listing of such neurologic disorders such as ALS, senile dementia, epilepsy, vascular headaches, presenile dementia, hyperkinesia, Tourette's syndrome, Parkinson's disease, stroke, attention deficit disorder, shizophrenia, chronic fatigue syndrome, etc. as well as neuropsychiatric disorders such as depression, anxiety, obsession, personality disorder, anorexia and bulimia. A number of treatments have been attempted to alleviate or cure these disorders, with varying degrees of success as summarized by the discussion in U.S. Patent No. 5,583,140. See, also, U.S. Patent Nos. 5,051,410; 5,069,904; 5,114,986; 5,171,745; 5,206,371; 5,242,935; 5,409,946; 5,434,179; 5,472,958; 5,589,512; 5,585,388; 5,696,142; and

5,703,100 which disclose varied treatments for central and peripheral nervous system disorders.

It is recognized that nervous system disorders may be due in large part to dysfunction of the nervous system itself. For example, an unbalancing of the neurotransmitters and neuroreceptors within the synapse as a result of cholinergic or dopaminergic defiencies may play a role in such disorders. However, to date no method of treatment has been provided which adequately rebalances the the neurotransmitters and neuroreceptors in a way which provides meaningful therapy in light of the potential effect of xenobiotic toxins (such as pesticides, fungicides, solvents, food additives, etc. as well as other environmental contaminants) has not been well-studied in relation to the occurrence and severity of central nervous system disorders.

It would accordingly be useful to provide a method for the treatment of central and autonomic nervous system disorders which addresses possible dysfunction of the nervous system itself with the effect that the previously-occurring symptoms are either eliminated or diminished in severity. Indeed, even a reduction of severity of such symptoms enhances the person's life.

The treatment of cardiac disorders and circulatory disease is commonplace. Such disorders include cardiac arrhythmias and related disorders of cardiac insufficiency. Various oximes and oxime derivatives are known to have pharmacological effect with respect to cardiac disorders and circulatory insufficiency. See, for example, U.S. Patent Nos. 3,875,149; 4,92,314; 4,461,763; 4,883,796; and 5,703,100. However, it

would be desirable to provide a method for treatment of cardiac disorders and circulatory insufficiency which provides enhanced effect.

The treatment of cancer by use of chemotherapy is presently commonplace. Such treatments may occur either alone or in conjunction with surgical removal of a tumor and/or radiation therapy. Such treatments are not without side effects to the patient. Chemotherapy agents which are toxic to cancer cells are also toxic to non-cancerous cells. The most susceptible cells of the patient are those having the highest rate of cell division; e.g., the bone marrow, hair and the gastrointestinal tract. A patient undergoing cancer treatment accordingly frequently suffers from nausea, vomiting, diarrhea, hair loss and lessened immune function (due to the lessened blood forming function of the bone marrow). It has also been found that administration of high levels of the therapeutic agent taxol may result in severe neurotoxicity in the form of peripheral neuropathy (see U.S. patent No. 5,496,804). Chemotherapeutic agents such as Adriamycin (doxorubicin hydrochloride) are also dose-limited due to the cardiotoxic effects of this agent.

Various methods have been proposed to lessen the toxic effects of antineoplastic disease treatment. See, for example, U.S. patent Nos. 4,581,224; 4,594,238; 4,620,973; 4,938,949; 4,980,149; 5,002,755; 5,035,878; 5,292,497; 5,294,430; 5,496,804; and 5,667,776.

Unfortunately, none of the above methods of treatment have been very successful. The degree of success of such methods is generally not

predictable due to the fact that the degree of success achieved is dependent upon the susceptibility of the patient to the particular treatment employed. In fact, it is now believed that some patients may be even more susceptible to the adverse effects of treatment of antineoplastic disease by chemotherapy and/or radiation due to factors such as comorbid addictions and environmental factors. It is believed, for example, that xenobiotic toxic agents such as pesticides, insecticides, fungicides, heavy metals, oxidants, solvents and other environmental toxins encountered by the patient by various means (e.g., drinking water, food contamination, etc.) may enhance the susceptibilty of the patient to the toxic effects of such treatment. Such xenobiotic agents place stress on the nervous system (both central and peripheral) by inhibiting the ability of the nervous system to efficiently transmit nerve impulses along the synapse. The treatment of such a patient for antineoplastic disease may accordingly accentuate the degree of diminishment of function of the patient's nervous system, and hence the side effects suffered by the patient. It would be desirable to provide a method by which such severe side effects are diminished.

It is well understood that obesity is a widespread problem. Obesity is linked to a variety of medical conditions including hypertension, diabetes, cardiovascular disease, etc. Obesity is also linked to a variety of psychological maladjustments. By contemporary medical standards an obese person is judged to be overweight by at least 10 percent. At present,

only a limited number of treatments are available to treat obesity. Exemplary treatments are disclosed in U.S. patent Nos. 3,867,539 (administration of histidine); 4,446,138 (administration of L-Dopa); 4,588,724 (administration of beta adrenergic stimulant or alpha-2 adrenergic inhibitor); 4,745,122 (administration of paroxetine); 5,019,594 (sympathomimetic drug and tyrosine); 5,300,298 (administration of 8-phenylxanthines); 5,403,851 (tryptamine); 5,567,714 (administration of neuropeptide Y); 5,573,774 (nicotinic metabolites); 5,578,613 (administration of 2-phenyl-3-aroylbenzothiophenes); 5,668,155 (muscarinic receptor antagonists); and 5,703,100 (acetylcholine receptor modulators). Amphetamine has also been used as an appetite suppressant.

Unfortunately, none of the above methods of treatment have been very successful. While such treatments may bring short-term relief to the person, long-term success has not been easily achieved. The cessation of tobacco use has frequently contributed to weight gain. Also, comorbid addictions, stress, psychiatric disorders and environmental factors may exacerbate the difficulty encountered by a particular person in alleviating obesity. It is believed, for example, that xenobiotic toxic agents such as pesticides, insecticides, fungicides, oxidants, solvents and other environmental toxins encountered by the person by various means (e.g., via drinking water and/or food impurities, etc.) may contribute to the inability of the person to control obesity. It is desirable to provide a method to assist in overcoming obesity.

Treatment of dysfunction of gastrointestinal motility and function, irritable bowel syndrome and related disorders is frequently necessary. For example, U.S. Patent No. 5,703,100 teaches the use of acetylcholine receptor modulators to treat such disorders. It is desirable to provide additional treatments which may provide enhanced results.

Fatigue syndromes are characterized by the fact that fatigue is a primary symptom with no underlying disease being determined to be the cause of the fatigue. Exemplary of such fatigue syndromes are Chronic Fatigue Syndrome, Post-infectious Fatigue Syndrome, chronic Epstein-Barr virus, and fatigue associated with human immunodeficiency virus (HIV) and total environmental allergy.

More specifically, Chronic Fatigue Syndrome has in recent years achieved much notoriety. It is estimated that 1 in 500 Americans may suffer from various of the symptoms of Chronic Fatigue Syndrome (CFS). CFS affects memory, mood, concentration, speech, sensation, balance, vision, hearing, sleep, appetite, hormone production and response to stress. Exemplary symptoms include chronic or relapsing severe fatigue, weakness, malaise, feverishness, sore throat, headaches, memory lapses, concentration difficulties, and depression. Various remedies have been attempted without much success, including exercise, special diets, vitamin therapy, antihistamines, immunoglobulins, antidepressants, etc. Exemplary treatments are disclosed in U.S. patent Nos. 5,013,739; 5,055,296; 5,189,022; 5,312,817; 5,424,300; and 5,545,670.

Interestingly, the symptoms of CFS closely resemble those of Gulf War Syndrome (suffered by many veterans of the Persian Gulf War). Prevalent symptoms include thought, memory and sleep disorders, confusion, dizziness, joint and muscle pain, tingling of hands and feet, etc. Alleviation of symptoms of Gulf War Syndrome (GWS) has not been any more successful than alleviation of symptoms of fatigue syndromes.

While not sharing all symptoms with fatigue syndromes and Gulf War Syndrome, other poorly defined conditions exist which share an inability to be successfully treated. Such conditions include Chronic Myofascitis and repetitive strain injury.

It is believed that such disorders may be due in large part to dysfunction of the central and autonomic nervous systems themselves. For example, an unbalancing of the neurotransmitters and neuroreceptors within the synapse as a result of cholinergic or dopaminergic defiencies may play a role in such disorders. However, to date no method of treatment has been provided which adequately rebalances the the neurotransmitters and neuroreceptors in a way which provides meaningful therapy. The potential effect of xenobiotic toxins (such as pesticides, fungicides, heavy metals, solvents, food additives, etc. as well as other environmental contaminants) as well as the combined effect of nerve gas antidotes, nerve gas exposure and pesticides has not been well-studied in relation to the occurrence and severity of such disorders. It is desirable to provide a method of treatment to diminish symptoms of CFS.

Toxic contaminants such as heavy metals are widely present in the environment. Such contaminants come into contact with mammals such as humans on a regular basis. Such heavy metals include lead, cadmium, mercury, iron and the like. Exemplary sources of such metals includes contaminated water, contaminated wildlife (such as fish), plumbing, paints, auto emissions, and manufacturing processes. Recently, questions have even been raised regarding the safety of mercury amalgam fillings in teeth. Unfortunately, the presence of such contaminants in the body leads to a variety of health problems, including mental disfunction, coronary problems, circulation problems, nervous system disfunction, etc.

Exemplary heavy metal detoxification treatments are disclosed in U.S. patent Nos. 2,847,308 (calcium salt of calcium chelate); 2,875,129 (calcium chelate); 2,947,782 (aminoacetamidoximes); 3,072,529 (5-aminohexahydro pyrimidine); 4,043,998 (1-(p-benzenediazonium)-ethylenediamine tetraacetic acid); 5,217,998 (soluble polymer substrate having chelate attached thereto); and 5,443,847 (soluble manganese salt). Unfortunately, none of the above methods of treatment have been totally successful and it would be desirable to provide a method which assists in not only removal of such materials but assists in alleviating symptoms of such poisons.

The treatment of cancer by use of chemotherapy is presently commonplace. Such treatments may occur either alone or in conjunction with surgical removal of a tumor and/or radiation therapy. Such treatments are not without side effects to the patient. Chemotherapy

agents which are toxic to cancer cells are also toxic to non-cancerous cells. The most susceptible cells of the patient are those having the highest rate of cell division; e.g., the bone marrow, hair and the gastrointestinal tract. A patient undergoing cancer treatment accordingly frequently suffers from nausea, vomiting, diarrhea, hair loss and lessened immune function (due to the lessened blood forming function of the bone marrow). It has also been found that administration of high levels of the therapeutic agent taxol may result in severe neurotoxicity in the form of peripheral neuropathy (see U.S. patent No. 5,496,804). Chemotherapeutic agents such as Adriamycin (doxorubicin hydrochloride) are also dose-limited due to the cardiotoxic effects of this agent. Indeed, various methods have been proposed to lessen the toxic effects of antineoplastic disease treatment. See, for example, U.S. patent Nos. 4,581,224; 4,594,238; 4,620,973; 4,938,949; 4,980,149; 5,002,755; 5,035,878; 5,292,497; 5,294,430; and 5,496,804.

Unfortunately, none of the above methods of treatment have been very successful. The degree of success of such methods is generally not predictable due to the fact that the degree of success achieved is dependent upon the susceptibility of the patient to the particular treatment employed. In fact, it is now believed that some patients may be even more susceptible to the effects of treatment of antineoplastic disease by chemotherapy and/or radiation due to factors such as comorbid addictions and environmental factors. It is believed, for example, that xenobiotic toxic agents such as pesticides,

insecticides, fungicides, heavy metals, oxidants, solvents and other environmental toxins encountered by the patient by various means (e.g., drinking water, food contamination, etc.) may enhance the susceptibilty of the patient to the toxic effects of such treatment. Furthermore, it is believed that xenobiotic agents may act synergistically to induce cancer by many mechanisms including immunologic, neuroimmunologic and/or neurologic dysregulation. In both the central and peripheral nervous system these xenobiotic agents inhibit the ability of the nervous system to efficiently transmit nerve impulses along the synapse. The treatment of neoplastic disease may be achieved by improving the efficiency of the synapse allowing for normalization of neurologic mechanisms and it would be desirable to provide a method of treatment which assists in neoplastic disease treatment by non-toxic means.

SUMMARY OF THE PRESENT INVENTION

In accordance with the present invention, there is provided a pharmaceutical composition for use in treatment of chronic symptoms in mammals including humans resulting from synaptic dysfunction and related disease disorders comprised of an effective amount of at least one pharmaceutically acceptable oxime which is physiologically active in vivo in mammals including humans such as an acetylcholine esterase reactivator optionally in association with an effective amount of one or more additional pharmacologically active agent together with a pharmaceutically acceptable carrier.

DETAILED DESCRIPTION OF THE PRESENT INVENTION

The pharmaceutical composition of the present invention may be used to treat a variety of chronic symptoms resulting from synaptic dysfunction and related disease disorders.

Synaptic dysfunction pertains to neurological disorders resulting from improper levels of neurotransmitter release, inappropriate properties of neurotransmitter receptors, and improper interaction between neurotransmitters and neurotransmitter receptors. Exemplary neurotransmitters and receptors include acetylcholine and acetylcholine receptors, respectively. Such dysfunction can also be attributed to cholinergic deficiencies, dopaminergic deficiencies, adrenergic deficiencies, and/or serotonergic deficiencies. It is believed inappropriate levels of deactivation of acetylcholine esterase and correspondingly inappropriate levels of acetylcholine in the synapse are responsible for many chronic symptoms of synaptic dysfunction.

Symptoms of synaptic dysfunction and related disease disorders include but are not limited to withdrawal symptoms due to the cessation of tobacco use, as well as chronic symptoms normally associated with respiratory disease, drug and alcohol addiction, disorders of the central and peripheral nervous systems, antineoplastic disease and the effects of antineoplastic disease treatment, eating disorders, cardiac disorders and circulatory insufficiency, fatigue syndromes, dysfunction of gastrointestinal motility and irritable bowel syndrome, endocrine and immune system disorders and heavy metal poisoning.

The oximes which are used in the present invention include the radical -C=NOH and are physiologically active in vivo. Such compounds for example, may exhibit one or more of the in vivo properties of cholinergic or muscarinic activity, anti-allergic, antihypertensive, antithrombotic, antiasthmatic, antiinflammatory, antirheumatic, or bronchodilator activity, cognitive or memory disorder-affecting activity, taste-affecting activity, and/or possess the ability to reactivate acetylcholine esterase which may have been deactivated due to organophosphate chemical poisoning. One or more oximes may be employed in the present invention.

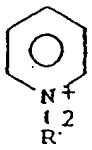
The oxime acetylcholine esterase reactivators which may be employed in the present invention are well known to those skilled in the art and well-described in the literature. Such reactivators found early use as nerve gas and toxic pesticide poisoning antidotes. Exemplary oxime acetylcholine esterase reactivators include but are not limited to those compounds disclosed in U.S. Patent Nos. 2,816,113; 2,996,510; 3,063,901; 3,077,476; 3,137,702; 3,773,775; 3,852,294; 3,928,594; 4,002,760; 4,128,651; 4,352,810; 4,675,326; 4,865,837; 4,925,856; 4,988,710; 5,130,438; 5,206,371 and U.K. application 2,016,920, each herein incorporated by reference in their entirety.

Additional oximes which may be used are prodrug derivatives thereof and pharmaceutically acceptable salts thereof.

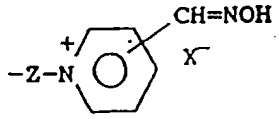
One exemplary class of oxime salts may be defined by the formula $(R^1\text{-}CR = NOH)^+ X^-$ where R is hydrogen, C_{1-5} alkyl, phenyl optionally substituted

with halogen, or NH_2 and X^- is a pharmaceutically acceptable anion derived from a salt of an inorganic or organic acid. The pharmaceutically-acceptable anions defined by X^- may be derived from hydriodic, hydrochloric, hydrobromic, sulfuric, sulfamic, phosporic, acetic, propionic, succinic, glycollic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfamilic, fumaric, toluenesulfonic, and related organic and inorganic acids. R^1 may take many forms. For example R^1 may be C_{1-5} alkyl, aryl (e.g., phenyl optionally substituted with C_{1-8} alkyl, hydroxy, halogen, C_{1-8} alkoxy, O-cycloalkyl, etc.), or a 5 or 6-membered heterocyclic moiety having from 1 to 3 nitrogen atoms in the heterocyclic ring which may be unsaturated or have varied degrees of saturation.

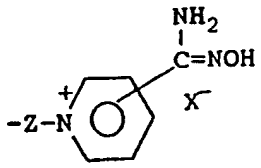
Another exemplary class of oxime salts is bicyclic in nature, as defined by the formula R^1-CR = NOH X^- where R is hydrogen, C_{1-5} alkyl or NH_2 and R^1 is



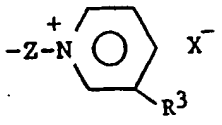
wherein R^2 is selected from the group consisting of:



;



; or



where Z is, for example, a polyalkylene group having from 1 to 10 carbon atoms, optionally including at least one ether linkage, such as -CH_2CH_2-, -CH_2OCH_2-, -$CH_2CH_2OCH_2CH_2$-, -$CH_2OCH_2CH_2OCH_2$-; butenylene; or -$(CH_2)_n$-phenyl-$(CH_2)_n$- where n ranges from 1 to 6 and the phenyl moiety may be substituted by C_{1-5} alkyl; where R^3 is hydrogen, C_{1-5} alkyl, COR^4, $CONR^5R^6$ or $COOR^7$ where R^4 is C_{1-6} alkyl, cyclohexyl, Ar or benzyl; R^5 and R^6 are hydrogen, C_{1-6} alkyl, cyclohexyl, Ar, C_{7-13} aralkyl or 2-pyrimidyl; and R^7 is C_{1-6} alkyl, cyclohexyl, benzyl or Ar; where Ar is phenyl optionally substituted with one or more of C_{1-4} alkyl, C_{1-6} alkoxy, halide or napthyl, and wherein X^- is a pharmaceutically acceptable anion derived from a salt of an inorganic or organic acid as defined above.

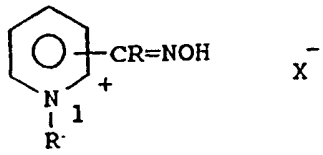
The above formulae are intended to be merely illustrative and not limiting of the identity of the various types of oximes that may be employed in the present invention.

Exemplary acetylcholine esterase reactivators include the following oximes and/or oxime salts:

2-pyridine aldoxime methiodide, 4-pyridine aldoxime methiodide, methyl-2-pyridyl ketoxime methiodide, 1-methyl-pyridinium-2-aldoxime (alternatively 2-formyl-1-methylpyridinium) (2-PAM); 1-methyl-pyridinium-3-aldoxime (3-PAM); 2,3-butanedione-2-oxime (DAM), pyruvaldehyde aldoxime (MINA), 2-formyl-1-methylpyridinium chloride (2-PAM-Cl) (pyridinium chloride marketed as PROTOPAM chloride), pralidoxime methylsulphate (marketed as CONTRATHION), N,N-dimethyleneoxy-bis-(pyridine-4-aldoxime)-dichloride (obidoxime chloride marketed as TOXOGONIN), 1,1'-polymethylene bis (4-formylpyridinium) halide oximes, N-methyl 2-hydroxyiminomethylpyridinium methane sulfonate, N-methyl 4-hydroxyiminomethylpyridinium methane sulfonate; 1,1'-(2,5-dimethyl-p-phenylenedimethylene) bis (4-formylpyridinium) halide dioximes; 1,1'-polymethylene bis (3-formylpyridinium) halide dioximes; 1,1'-(p-phenylenedimethylene) bis (3-formylpyridinium) halide dioximes; bis quaternary 4-formylpyriinium halide monooximes; 1,1'trimethylene bis (3-amidooximopyridinium) halides, quaternary pyridine aldoxime (TMB-4); 1-[[[4-(aminocarbonyl)pyridino]methoxy]methyl]-2-[(hydroxyimino)methyl]pyridinium dichloride (Asoximine chloride or HI-6); diacetyl monoxime; [(2-hydroxyiminomethyl)-pyridinium-(1)-methyl]-[(3-carbamoyl)-pyridinium-(1)-methyl]-ether dichloride (HS-6); aldoxime-substituted triazolium compounds including 3-(hydroxyimino)methyl-1-methyl-4-(2'-methylsulfonyl-1-ethyl)-1,2,4-triazolium chloride; 1,4-dimethyl-3-(hydroxyimino)methyl-1,2,4-triazolium chloride, 1-benzyl-3-(hydroxyimino)methyl-4-methyl-1,2,4-

triazolium chloride, and 3-(hydroxyimino)methyl-1-methyl-4-(2'-methylsulfonyl-1'-ethyl)-1,2,4-triazolium chloride; and aldoxime-substituted imidazolium derivatives such as 1-([1'-(2'-butynyloxy)methyl]-2-(hydroxyimino)methyl-3-methylimidazolium chloride, 2-(hydroxyimino)methyl-3-methyl-1-[1'-2'-(methylsulfonyl)ethyloxy)methyl)-imidazolium chloride, 2-(hydroxyimino)methyl-3-methyl-1-[(2'-methyl-2'-nitropropyloxy)methyl]-imidazolium chloride, 1-[(2'-N,N-dimethylaminium)-1'-ethyl]2-(hydroxyimino)methyl-3-methylimidazolium chloride, 1-[2'-(hydroxyimino)methyl-3'-methyl-1'-imidazolo]-3-(4''-carbamoyl-1''-pyridino)propane dichloride, 1-(3'-bromopropyl-1'-oxy)methyl-2-(hydroxyimino)methyl-3-methylimidazolium chloride, 2-(hydroxyimino)methyl-3-methyl-1-(2'-pyrrdidinium-1'-)ethylimidazolium chloride hydrochloride, 1-(3'-butynyl-1'-thio)methyl-2-(hydroxyimino)methyl-3-methylimidazolium chloride, and 1-[(2'-N-ethyl-N-trifluoromethane sulfonyl)amino-1'-]ethyl-2-hydroxyimino)methyl-3-methylimidazolium chloride.

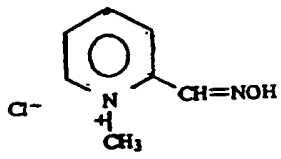
A preferred class of oximes suitable for use in the present invention may be depicted by the formula:



wherein R is hydrogen, C_{1-5} alkyl,or NH_2; R^1 is C_{1-5} alkyl (particularly methyl or ethyl), and X is an anion portion of the salt R^1X. Preferred acid addition salts include the chloride salt, the

iodide salt and C_{1-5} alkyl sulfonate salts such as the methanesulfonate salt.

A specific oxime which is preferred for use in the present invention is 2-PAM chloride (PROTOPAM Chloride, pralidoxime chloride) which is depicted by the following formula:



Obidoxime is also a particularly preferred oxime for use in the present invention.

It is also advantageous to administer prodrug derivatives of oximes as disclosed in U.S. patent Nos. 3,929,813 and 3,962,447. Such prodrug derivatives exhibit an enhanced ability to pass the blood/brain barrier.

Additional oximes which exhibit physiological properties in vivo and which may be used in the present invention are described in U.S. Patent Nos. 3,780,194; 3,875,149; 3,883,654; 3,919,318; 3,952,114; 4,141,995; 4,678,810; 4,798,841; 4,816,487; 5,026,724; 5,219,872; 5,650,444; and 5,693,659.

Acetylcholine esterase reactivators (such as 2-PAM and HI-6) have been used in conjunction with acetylcholine receptor antagonists (such as atropine) to provide in vivo protection against nerve gas agents and other organophosphate poisons. See, for example, U.S. patent Nos. 2,996,510; 3,063,901; 3,077,476; 4,128,651; 4,713,391; 4,865,837; and 4,925,856. Atropine (an acetylcholine receptor antagonist) has also been

used to treat bronchitis, nasal inflammation, hay fever, etc. as discussed in U.S. Patent No. 1,794,292.

However, a pharmaceutical composition comprised of a physiologically active oxime such as an acetylcholine esterase reactivator (optionally together with an additional pharmacological active agent such as an acetylcholine receptor antagonist) has not previously been employed to alleviate the chronic symptoms of synaptic dysfunction and related disease disorders as may be associated with, for example, withdrawal symptoms due to cessation of tobacco use as well as other types of chronic symptoms of synaptic dysfunction. Indeed, the amounts of the respective components required to provide the benefits of the present invention are orders of magnitude less than the amounts normally administered to provide protection against nerve gas agents or toxic organophosphate poisoning.

In accordance with the present invention, the active agent may optionally be employed with one or more additional pharmacological active agents. It is within the scope of the present invention to co-administer additional compounds to assist in achieving the desired result or to provide additional cooperative treatment. The selection of co-administrable compound(s) depends upon which chronic symptoms are to be addressed.

Such additional agents are varied in type and pharmacological effect. The choice of additional pharmacological agent depends upon the particular symptoms to be alleviated. Exemplary additional pharmacological agents include but are not limited to cholinergic agents (such as nicotinic and

muscarinic agonists and antagonists), adrenergic agonists and antagonists, serotonergic active agents, GABA agonists and antagonists, adenosine active agents, dopaminergic active agents, antiinflammatories, stimulants, heavy metal antagonists and chelating agents, acetylcholine esterase inhibitors, anti-allergenics, anti-hypertensives, anti-thrombotics, anti-asthmatics, anti-rheumatics, anti-depressants, anti-obesity agents, anti-epileptics, antioxidants, anti-arrythmics, anti-anginal agents, calcium channel blockers, bronchodilators, cognitive or memory disorder enhancers, antineoplastic disease treatment agents, vitamins, nutritional supplements, cardioactive agents, and binding resins, etc.

The acetylcholine receptor antagonists which may optionally be employed in the present invention are well known to those skilled in the art and well-described in the literature. Exemplary antagonists include but are not limited to (singly or in combination) scopolamine, homatropine, atropine, methscopolamine, methylatropine, ipratropium, methylecgonidine (MEG), mecamylamine, benactyzine, benztropine, trihexyphenidyl, biperiden, procyclidine, benzetimide, dexetimide, iaprophen and pharmaceutically acceptable derivatives thereof, as well as mixtures thereof. See, for example, U.S. patent Nos. 5,011,853 and 5,552,407, which disclose exemplary acetylcholine receptor antagonists. Preferred antagonists are scopolamine and ipratropium. Anticholinergic agents such as ipratropium bromide (Atrovent) are known for use with the treatment of

bronchoconstriction. See, Goodman & Gilman's The Pharmacological Basis of Therapeutics, 5th Edition, 1996.

By way of further example, depending upon the severity of the chronic symptoms of synaptic dysfunction which pertain to respiratory disease such as asthma,. it may be desirable to also administer an anti-asthmatic drug. Exemplary anti-asthmatic drugs include (1) anti-antiinflammatory drugs such as corticosteroids (Beclomethasone dispropionate, Budesonide, Flunisolide, Triamcinolone acetonide, Prednisone, etc.), Cromolyn, and Nedocromit, and (2) bronchodilators such as B_2-selective adrenergic drugs (Albuterol, Bitolterol mesylate, Pirbuterol, Salmeterol and Terbutaline) and Theophylline.

By way of further example, it may be advantageous to administer a stimulant in association with the cholinesterase reactivator, especially if the symptoms of tobacco use cessation are to be treated. A preferred stimulant is nicotine. Nicotine may be administered by any appropriate means, including coadministration with the active ingredient(s), nicotine gum, a nicotine patch, etc. Nicotine administration may occur prior to, during or subsequent to administration of the other compounds. It has been found that the amount of nicotine administered is less than the amount found in a patch or a stick of nicotine gum (e.g., one milligram or so, the amount not being particularly critical) when treating tobacco addiction. The administration of nicotine or other stimulant may also be useful in certain

other treatments of symptoms of other related diseases such as asthma.

Other conventional stimulants (such as dopaminergic stimulants) may be administered in lieu of or in addition to nicotine. Such alternative stimulants include but are not limited to mineptine, Amphetimine, Amphetaminil, Bemegride, Benzphetamine, Brucine, Chorphentermine, Clofenciclan, Clortermine, Cocoa, Demanyl Phosphate, Dexoxadrol, Dextroamphetamine Sulfate (Dexedrine), Diethpropion, N-Ethylamphetamine, Ethamivan, Etifelmin, Etryptamine, Fencamfamine, Fenethylline, Fenosolone, Fenfluramine, Flurothyl, Hexacyclonate Sodium, Homocamfin, Mazindol, Megexamide, Methamphetamine, Methylphenidate, Nicotinic agonists, Nikethamide, Pemoline, Pentylenetetrazole, Phenidimetrazine, Phenmetrazine, Phentermine, Picrotoxin, Pipradrol, Prolintane, Pyrovalerone, and Tetrahydrobenzothienopyridines and mixtures thereof.

Xanthines are an additional class of compounds that may be administered in conjunction with the acetylcholine esterase reactivator and one or more of the other optional active ingredients to assist in signal modulation along the dendrite. U.S. patent Nos. 4,364,922; 4,980,379; 5,288,721; 5,340,813; 5,354,756; 5,440,041; 5,473,070; 5,567,704; 5,580,873; and 5,580,874 disclose exemplary xanthines which may be used in the present invention, each herein incorporated by reference. Exemplary xanthines include but are not limited to alkylxanthines such as propylxanthine and methylxanthine.

Methylxanthines include 1,3,7-trimethylxanthine (caffeine), 3,7-dimethylxanthine (theobromine), 1,3-dimethylxanthine (theophylline), aminophylline, 1,8-dimethyl-3-(2-methyl-1-butyl)xanthine, 1,3-dimethyl-8-(n-propyl)xanthine, 1,4-(4-hydroxypentyl)-3,7-dimethylxanthine, and 7-(3-phenylpropenyl)theophylline. Exemplary propylxanthines include (E)-4-(1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-9H-purin-8-yl)cinnamic acid and (E)-4-(1,2,3,6-tetrahydro-2,6-dioxo-1,3-dipropyl-9H-purin-8-yl)cinnamic acid. Prodrug forms of xanthines may also be employed as disclosed in U.S. patent Nos. 3,935,196 and 4,061,753, herein incorporated by reference. Such forms exhibit enhanced lipid solubility of the compound.

Adenosine antagonists may also be employed in conjunction with one or more of the above. Such compounds reduce the interstitial concentration of adenosine in myocardial tissue. The compounds may either be a competitive inhibitor or a substance that reduces the concentration of adenosine. A variety of compounds may be used as adenosine antagonists including xanthines (such as those discussed above), imidazopyrimidine, pyraxolopyridine, etazolate, pyrazoloquinoline and triazoloquinazoline. Exemplary adenosine antagonists are described in U.S. patent Nos. 4,364,922; 4,980,379; and 5,364,922, each herein incorporated by reference.

As still yet another compound which may be administered in conjunction with one or more of the above is the inhibiting neurotransmitter gamma-aminobutyric acid (GABA) or a precursor thereof such as L-glutamic acid. GABA receptor

agonists and other antiepileptics may be employed such as Epival, Baclofen, Sabril, barbiturates, Gabapentin, Lamotrizine and Riluzolo.

It may also be useful to additionally administer an acetylcholine esterase inhibitor such as Phytostigmine, Neostigmine, Demecarium, Pyridostigmine, Velnacrine, Huperzine A, Tacrine, Aricept (Donepezil hydrochloride), Memric, Artane (trihexyphenidyl), Cogentin (benzotropine mesylate), Benedryl (diphenhydramine hydrochloride), Donepezil hydrochloride, etc.

It is also within the scope of the present invention to combine administration of the active ingredients with more conventional therapies such as antioxidant treatment, vitamin treatment, heavy metal antagonists such as chelating agents and bile-acid binding resins. The identity of such compounds is well known to those skilled in the art as described in Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th edition, 1996.

It is within the scope of the present invention to employ both pharmaceutically acceptable prodrugs, analogs as well as tautomers, isomers and salts of the above listed compounds. Analogs differ from the above compounds by means of added alkyl or aryl substituents, added or deleted halogen moieties, presence of differing linkages such as ether linkage, saturation or unsaturation. As to possible salts, the present invention includes within its scope salts of alkali metals, alkaline earth metals, as well as acid addition salts of hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, acetic, propionic, succinic, glycollic, stearic, lactic, malic,

tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, fumaric, etc.

The compounds of the present invention may be administered by any pharmaceutically acceptable means and in any pharmaceutically acceptable form. For instance, the compounds may be administered orally in the form of pills, tablets, capsules, granulates, suspensions, syrups, lozenges, etc. in which the compound is the sole or co-ingredient as the active agent. The compounds may also be administered parenterally (e.g., intravenously, intramuscularly or subcutaneously) in association with a pharmaceutically acceptable carrier. Topical administration may be accomplished by various means such as by transdermal patch or administration in conjunction with a suitable pharmaceutically acceptable topical base carrier such as an ointment, cream or salve which provides for percutaneous penetration of the active agent into the skin. Such percutaneous penetration may be accomplished by percutaneous penetration enhancers which are well-known for use in connection with transdermal administration of pharmacological agents by topical administration. From the standpoint of an ointment, salve or cream, dimethyl sulfoxide (DMSO) is an acceptable percutaneous penetration enhancer, especially in an veterinary environment. The active components may also be administered by inhalers, internasally or rectally by suppository or by enema.

The solid carrier material for use with tablets and/or pills may be any pharmaceutically acceptable solid carrier material which may be mixed with the active ingredient(s) and compacted

in the shape and size desired. Suitable carriers include but are not limited to magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, methyl cellulose, sodium carboxymethyl cellulose, etc.

Tablets or pills may contain the active ingredient(s) in admixture with conventional pharmaceutically acceptable excipients (i.e., inert diluents). Such tablets or pills may be uncoated or coated. Such tablets or pills may include an enteric coating to ensure disintegration and absorption in the intestine. Such coatings are generally comprised of a cellulose lower fatty acid phthalate such as cellulose acetate phthalate. Slow release forms of oral administration are also contemplated and may be desirable.

It is preferred that the pharmaceutical composition be administered in an oral dosage form which comprises the active ingredient(s) in a pharmaceutically acceptable solid matrix material capable of dissolution and/or disentegration in the mouth to permit sublingual or buccal delivery of the active ingredient(s).

The oxime (and optionally one or more additional pharmacologically active agents) are employed or administered in an amount effective to reduce or prevent the chronic symptoms of synaptic dysfunction or related disease disorders.

For example, when administered to alleviate the symptoms of tobacco withdrawal, the active ingredient(s) are administered in an amount effective to reduce or prevent the physiological and psychological effects of tobacco withdrawl due to diminished or non-use of tobacco. The phrase

"reduce or prevent" is intended to refer to any degree of reduction of the symptoms of withdrawal suffered by the person, as well as any degree of prevention of the suffering of such symptoms if administered prior to the onset of such symptoms. That is, the present invention may be used prophylactically as well as to treat presently existing withdrawal symptoms resulting from cessation of tobacco use.

With the above in mind, the various compounds of the present invention may be administered within a wide range of dosage levels while still enabling the benefits of the present invention to be achieved. For example, when an acetylcholine receptor antagonist is employed, it is generally administered at a dosage level of from about 0.001 to 100 mg, preferably at a dosage level of from 0.001 to 25 mg, more preferably 0.001 to 10 mg. The oxime such as the acetylcholine esterase reactivator may, for example, be administered at a dosage level of from about 1.0 mg to 10 grams. Generally, however, the acetylcholine esterase reactivator will be administered in an amount of from 0.1 to 300 mg., and more generally from 0.1 to 25 mg. A dosage level of acetylcholine esterase reactivator of from 0.1 to 10 mg (sublingual or buccal) has been found to be useful in the treatment of various chronic symptoms such as tobacco withdrawal symptoms, optionally in association with a dosage level of acetylcholine antagonist of from 0.001 to 0.1 mg. Such dosage levels are based on a standard adult body weight of 70 kg. Additional components such as stimulants are generally administered in dosage amounts of from about 0.1 to 10 mg. The xanthine

component, if administered, will generally be administered in a dosage amount of from 25 to 300 mg. Other components that may be co-administered may be administered in conventional dosage amounts as determined by the particular symptoms to be addressed. Such dosage administrations are repeated as required to provide the desired results, with administrations being repeated every 4 to 36 hours or longer depending upon the extent of symptoms observed.

The pharmaceutical composition of the present invention finds particular applicability in the control and/or reduction of tobacco use of any type. Such tobacco use may result from smoking (i.e., by cigarettes, cigars or pipes) or by use of smokeless or chewing tobacco. It has been found that of the various methods of tobacco use, chronic cigarette and smokeless or chewing tobacco use have been the most difficult to control or cease. Indeed, if begun during the teenage years, such use has been found in the past to be particularly difficult to control or cease. However, by administration of the pharmaceutical composition of the present invention it is possible for a person who desires to control or cease such use to achieve this goal with a high likelihood of success.

The pharmaceutical composition of the present invention may be used to treat both animals and humans. Veterinary treatment of animals has not always met with success when attempting to alleviate chronic symptoms of synaptic dysfunction. This is believed to be particularly true with respect to farm animals which may be periodically exposed to pesticides and/or

herbicides. In fact, horses are frequently in need of treatment for respiratory disease such as asthma. Other livestock such as sheep frequently encounter pesticides which may lead to chronic symptoms of synaptic dysfunction. Domestic animals such as dogs and cats also frequently suffer from chronic symptoms of synaptic dysfunction due to exposure to residential pesticides and herbicides and/or other xenobiotic contaminants. Topical administration of the oxime (together with other optional active ingredients) in conjunction with a suitable topical carrier which facilitates percutaneous adsorption of the active ingredient (such as DMSO) finds particular utility in the veterinary treatment of mammals.

The present invention is illustrated by the following examples which are not intended to be limiting of the scope of the invention but merely illustrative of various preferred and specific embodiments.

EXAMPLE 1

A forty year old male with a twenty five year smoking history of moderate intensity and a desire to cease smoking cigarettes was administered via the oral mucosa by drops an acetylcholine receptor antagonist (scopolamine) followed by oral administration of an oxime acetylcholine esterase reactivator (2-PAM-Cl), each in a pharmaceutically acceptable solution. A nicotine patch was placed on the person's torso immediately prior to the administration of the two compounds. The scopolamine was administered within the dosage range of from 0.001 to 10 mg. and the 2-PAM-Cl was administered within the dosage range of from 2 to

8 mg. The person experienced a relatively immediate lack of desire to use tobacco (in this instance the smoking of cigarettes). The ability to control the desire to smoke a cigarette continued for 8 hours. Similar results were observed upon sublingual administration of the two compounds in the form of a tablet. The administration of nicotine in chewing gum form at the time of administration of the two compounds was also found to be effective.

EXAMPLE 2

A 39 year old male smoker (1-2 packs per day) with a 25-30 pack year smoking history was highly motivated to quit smoking. He was given 5 mgs of the oxime Protopam on multiple occasions following either (1 mg nicotine and 0.1 mg scopolamine) or (1 mg nicotine and 0.1 mg ipratropium) via the oral mucosa by drops and gum. The individual reported that he remained withdrawal symptom free for periods of time ranging from 6-36 hours. As a followup, he was placed on a lozenge containing 0.1 mg of either ipratropium or scopolamine with Protopam 2.5 mg. On a bid dosage of either lozenge combined with a nicotine patch he was able to remain smoke free without any significant withdrawal symptoms or urges to smoke for the ten day trial period.

EXAMPLE 3

A 35 year old male (1.5 pack/day smoker) with a 30 pack year smoking history was given 5 mg of Protopam following 0.1 mg ipratropium and 1 mg of nicotine sub lingual (sl) before his first cigarette of the day at 8:00 a.m. He reported that he had not normally lasted more than 20 minutes upon awakening before his first cigarette of the day in the previous 5 years. On the day of this medical trial he managed until 3:00 p.m. before having his first cigarette. By 5:00 p.m. he had attempted to smoke 3 cigarettes but found them to be too strong and much less satisfying than normal. A second dose sequenced in the same fashion was administered at 6:00 p.m. with the patient stating with surprise that he felt more satisfied than with the cigarettes earlier in the day. A third dose of just Protopam (5 mg) was given at 10:00 p.m. The subject reported at that time a feeling of deep satisfaction and a clarity of mind.

EXAMPLE 4

A 37 year old male smoker desired to quit smoking. He had a 25 pack year smoking history and continued to smoke 12 cigarettes/day. This person also suffered from Wolf Parkinson White syndrome complicated by frequent irregular rapid heart rate and intermittent atrial fibrillation. He also suffered from a chronic myofascial syndrome characterized by diffuse muscle spasms and recurrent tendonitis. The person was given 5 mg Protopam (sl) following 1 mg nicotine and 0.01 mg ipratropium on 4 occasions. On each occasion he reported a release of the need for a cigarette

within 1 to 2 minutes of receiving the Protopam as well as an attenuation of his myofacial syndrome and improved regularity of his heart rate lasting 2 to 5 days.

EXAMPLE 5

A 24 year old female with a 10 year half pack/day smoking history stated that she smoked partially to control her weight. She was given 1 mg nicotine and 0.01 mg of ipratropium followed by 2.5 mg of Protopam in sequence on 10 occasions over a period of 2 months by the oral mucosa route of administration. On each occasion she reported relief from withdrawal symptoms and a feeling of satisfaction lasting 6 to 12 hours with no side effects. The "satisfaction" was reported as deep as that of a cigarette but longer lasting. Relief of negative symptoms such as calf muscle cramps, restricted breathing (bronchospasm and bronchial secretions), nasal congestion and fatigue were also reported. On 2 occasions the sequenced drug trial was administered before lunch and dinner on separate days when the person was "due" for her next cigarette. On both occasions, she reported not only that the need for a cigarette was extinguished but that her appetite was diminished as was her cravings for sweets.

EXAMPLE 6

A 24 year old female with a 10 year half pack/day smoking history stated that she smoked partially to control her weight. She was given 1 mg nicotine and 0.01 mg of ipratropium followed by 2.5 mg of Protopam in sequence on 10 occasions over a period of 2 months by the oral mucosa route

of administration. Relief of negative symptoms such as calf muscle cramps, restricted breathing (bronchospasm and bronchial secretions), nasal congestion and fatigue were reported.

EXAMPLE 7

A 39 year old female with mild asthma and allergies was given 5 mg. of Protopam following 0.01 mg. of ipratropium on 3 occasions by an oral mucosa route of administration when feeling "chesty and nasal". Following each sequential trial a relief of symptoms was reported which lasted for 12 to 36 hours.

EXAMPLE 8

A 35 year old male competitive fitness trainer with mild asthma and allergies and chronic muscle strain described as a tightness about his neck, shoulders and upper back had consulted unsuccessfully with professionals of other disciplines for relief. The patient was given 5 mg. of Protopam sl following 1 mg of nicotine and 0.01 mg of ipratropium by the oral mucosa route on 2 different occasions. Following each administration the patient reported profound relief of his symptoms lasting approximately 4 days.

EXAMPLE 9

A 71 year old male with documented early memory loss on multiple vitamin, mineral and antioxidant therapy (self medication) was given 2.5 mg of Protopam sl with reported improved memory concentration and diminished agitation and mental "fogginess" as verified by other family

members. The beneficial effects lasted 3 to 5 days.

EXAMPLE 10

A 67 year old female moderately obese ex-smoker suffering from presenile dementia was given a trial of Protopam 2.5 mg. sl. The patient had been on low dose valproic acid 125 mg. bid and had been using a nicotine patch on a bi-weekly basis for the preceding 2 years. Upon administration of the sl Protopam, she reported a "clearing of her mind" and a diminished appetite lasting 5 to 7 days. The findings were reproduced on 3 separate occasions over a 6 week period as verified by family members.

From the above description, one of ordinary skill in the art can readily ascertain the essential characteristics of the present invention. Without departing from the scope of the present invention, various changes and/or modifications can be made which are still within the scope and range of equivalents of the attached claims.

I CLAIM:

1. A unit drug dosage form for administering to a mammal including humans for alleviating chronic symptoms of synaptic dysfunction and related disease disorders comprising in combination as active agents in a pharmaceutically acceptable carrier (1) at least one pharmaceutically acceptable oxime which is physiologically active in vivo in the mammal, and (2) an effective amount of at least one additional pharmacologically active agent, said oxime being present in said dosage form in an amount sufficient to provide a dosage of from 0.1 mg to 10 gm/70 kg body weight.

2. A pharmaceutical composition for administration to a mammal including humans for alleviating chronic symptoms of synaptic dysfunction and related disease disorders comprising an effective amount of at least one pharmaceutically acceptable oxime which is physiologically active in vivo in the mammal optionally together with an effective amount of at least one additional pharmacologically active agent in a pharmaceutical carrier suitable for topical administration of said active ingredients to said mammal.

3. In a transdermal drug delivery system for administering a pharmacological agent to a mammal including humans by means of a patch applied to the skin of said mammal, the improvement wherein said delivery system includes an effective amount of at least one pharmaceutically acceptable oxime

which is physiologically active in vivo in the mammal optionally together with an effective amount of at least one additional pharmacologically active agent for administration of said active ingredients to said mammal for alleviating chronic symptoms of synaptic dysfunction and related disease disorders.

4. The product of claims 1-3 wherein said at least one additional pharmacologically active agent is selected from the group consisting of cholinergic agents, adrenergic agonists and antagonists, serotonergic active agents, GABA agonists and antagonists, adenosine active agents, dopaminergic active agents, antiinflammatories, stimulants, heavy metal antagonists and chelating agents, acetylcholine esterase inhibitors, anti-allergenics, anti-hypertensives, anti-thrombotics, anti-asthmatics, anti-rheumatics, anti-depressants, anti-obesity agents, anti-epileptics, antioxidants, anti-arrythmics, anti-anginal agents, calcium channel blockers, bronchodilators, cognitive or memory disorder enhancers, antineoplastic disease treatment agents, vitamins, nutritional supplements, cardioactive agents, binding resins, and mixtures thereof.

5. The product of claim 4 wherein said additional pharmacologically active agent is an acetylcholine receptor antagonist.

6. The product of claims 1-5 wherein said acetylcholine receptor antagonist is selected from

the group consisting of scopolamine, homatropine, atropine, methscopolamine, methylatropine, ipatropium, mecamylamine and mixtures thereof.

7. The product of claims 1-6 wherein said oxime is an acetylcholine esterase reactivator, a pharmaceutically acceptable prodrug derivative thereof, or a pharmaceutically acceptable salt thereof.

8. The product of claims 1-7 wherein said oxime is selected from the group consisting of 1-methyl-pyridinium-2-aldoxime (2-PAM), obidoxime, 2,3-butanedione-2-oxime (DAM), pyruvaldehyde aldoxime (MINA), bis quaternary pyridine aldoxime (TMD-4), pharmaceutically acceptable prodrug derivatives thereof and pharmaceutically acceptable salts thereof.

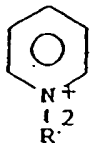
9. The product of claims 1-8 wherein said at least one additional active agent comprises a stimulant.

10. The product of claim 9 wherein said stimulant is selected from the group consisting of nicotine, muscarine, arecoline, lobeline, cotinine, kat, nikethamide, ethamivan, bethanechol, pilocarpine, and mixtures thereof.

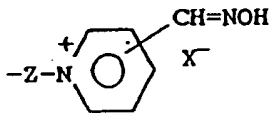
11. The product of claims 1-10 wherein said oxime is defined by the formula $(R^1\text{-}CR = NOH)^+ X^-$ where R is hydrogen, C_{1-5} alkyl, optionally substituted phenyl, or NH_2, R^1 is C_{1-5} alkyl, aryl, or a 5 or 6 membered heterocyclic moiety having from 1 to 3 nitrogen atoms in the heterocyclic

ring and X^- is a pharmaceutically acceptable anion derived from a salt of an inorganic or organic acid.

12. The product of claims 1-10 wherein said oxime is defined by the formula R^1-CR = NOH X^- where R is hydrogen, C_{1-5} alkyl, optionally substituted phenyl, or NH_2 and R^1 is



wherein R^2 is selected from the group consisting of:



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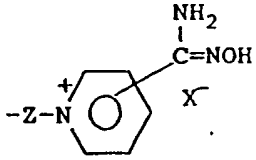
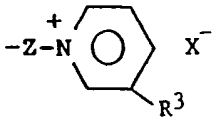


; or



where Z is a polyalkylene group having from 1 to 10 carbon atoms, optionally including at least one

ether linkage, butenylene, or -(CH_2)n-phenyl-(CH_2)n- where n ranges from 1 to 6 and the phenyl moiety may be optionally substituted by C_{1-5} alkyl, where R^3 is hydrogen, C_{1-5} alkyl, COR^4, $CONR^5R^6$ or $COOR^7$ where R^4 is C_{1-6} alkyl, cyclohexyl, Ar or benzyl; R^5 and R^6 are hydrogen, C_{1-6} alkyl, cyclohexyl, Ar, C_{7-13} aralkyl or 2-pyrimidyl; and R^7 is C_{1-6} alkyl, cyclohexyl, benzyl or Ar; where Ar is optionally substituted phenyl and wherein X^- is a pharmaceutically acceptable anion derived from a salt of an inorganic or organic acid.

13. The product of claim 1 wherein said oxime is administered in an amount within the range of from about 0.1 to 300 mg per 70 kg body weight.

14. The product of claim 13 wherein said oxime is administered in an amount within the range of from about 0.1 to 25 mg per 70 kg body weight.

15. The product of claim 1 wherein said pharmaceutically acceptable carrier dissolves and/or disintegrates in the mouth to permit sublingual or buccal administration.

16. The product of claim 1 in the form of a pill, tablet, granulate, syrup, lozenge, capsule, injectable solution, ointment, cream, salve, suppository or transdermal patch.

17. The product of claim 2 in the form of an ointment, cream or salve, optionally containing dimethyl sulfoxide (DMSO).

18. The use of a pharmaceutically acceptable oxime which is physiologically active in vivo in mammals including humans to alleviate chronic symptoms of synaptic dysfunction and related disease disorders in a mammal including humans.

19. The use of claim 18 together with at least one additional pharmacologically active agent.

20. The use of claim 19 wherein said at least one additional pharmacologically active agent is selected from the group consisting of cholinergic agents, adrenergic agonists and antagonists, serotonergic active agents, GABA agonists and antagonists, adenosine active agents, dopaminergic active agents, antiinflammatories, stimulants, heavy metal antagonists and chelating agents, acetylcholine esterase inhibitors, anti-allergenics, anti-hypertensives, anti-thrombotics, anti-asthmatics, anti-rheumatics, anti-depressants, anti-obesity agents, anti-epileptics, antioxidants, anti-arrythmics, anti-anginal agents, calcium channel blockers, bronchodilators, cognitive or memory disorder enhancers, antineoplastic disease treatment agents, vitamins, nutritional supplements, cardioactive agents, binding resins, and mixtures thereof.

21. The use of claim 19 wherein said at least one additional active agent is an acetylcholine receptor antagonist.

22. The use of claim 21 wherein said acetylcholine antagonist is selected from the

group consisting of scopolamine, homatropine, atropine, methscopolamine, methylatropine, ipatropium, mecamylamine and mixtures thereof.

23. The use of claims 18-22 wherein said oxime is an acetylcholine esterase reactivator, a pharmaceutically acceptable prodrug derivative thereof, or a pharmaceutically acceptable salt thereof.

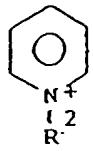
24. The use of claims 18-23 wherein said oxime is selected from the group consisting of 1-methyl-pyridinium-2-aldoxime (2-PAM), obidoxime, 2,3-butanedione-2-oxime (DAM), pyruvaldehyde aldoxime (MINA), and bis quaternary pyridine aldoxime (TMD-4).

25. The use of claims 18-24 in combination with a stimulant.

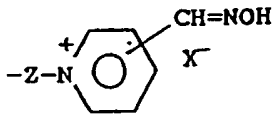
26. The use of claim 25 wherein said stimulant is selected from the group consisting of nicotine, muscarine, arecoline, lobeline, cotinine, kat, nikethamide, ethamivan, bethanechol, pilocarpine, and mixtures thereof.

27. The use of claims 18-26 wherein said oxime is defined by the formula $(R^1\text{-}CR = NOH)^+ X^-$ where R is hydrogen, C_{1-5} alkyl, optionally substituted phenyl, or NH_2, R^1 is C_{1-5} alkyl, aryl, or a 5 or 6 membered heterocyclic moiety having from 1 to 3 nitrogen atoms in the heterocyclic ring and X^- is a pharmaceutically acceptable anion derived from a salt of an inorganic or organic acid.

28. The use of claims 18-26 wherein said oxime is defined by the formula R^1-CR = NOH X^- where R is hydrogen, C_{1-5} alkyl, optionally substituted phenyl, or NH_2 and R^1 is



wherein R^2 is selected from the group consisting of:



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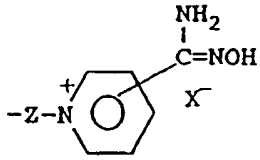
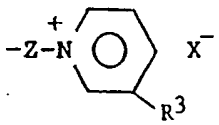


; or



where Z is a polyalkylene group having from 1 to 10 carbon atoms, optionally including at least one

ether linkage, butenylene, or -(CH_2)n-phenyl-(CH_2)n- where n ranges from 1 to 6 and the phenyl moiety may be optionally substituted by C_{1-5} alkyl, where R^3 is hydrogen, C_{1-5} alkyl, COR^4, $CONR^5R^6$ or $COOR^7$ where R^4 is C_{1-6} alkyl, cyclohexyl, Ar or benzyl; R^5 and R^6 are hydrogen, C_{1-6} alkyl, cyclohexyl, Ar, C_{7-13} aralkyl or 2-pyrimidyl; and R^7 is C_{1-6} alkyl, cyclohexyl, benzyl or Ar; where Ar is optionally substituted phenyl and wherein X^- is a pharmaceutically acceptable anion derived from a salt of an inorganic or organic acid.

29. The use of claims 18-28 wherein said oxime is administered in an amount within the range of from about 0.1 mg to 10 grams per 70 kg body weight.

30. The use of claim 29 wherein said oxime is administered in an amount within the range of from about 0.1 to 300 mg per 70 kg body weight.

31. The use of claims 21-22 wherein said acetylcholine receptor antagonist is administered in an amount within the range of from about 0.001 to 100 mg per 70 kg body weight.

32. The use of claim 31 wherein said acetylcholine receptor antagonist is administered in an amount within the range of about 0.001 to 25 mg per 70 kg body weight.

33. The use of claims 18-32 together with a pharmaceutically acceptable carrier which dissolves and/or disintegrates in the mouth to permit sublingual or buccal administration.

34. The use of claims 18-32 in the form of a pill, tablet, granulate, syrup, lozenge, capsule, injectable solution, ointment, cream, salve, suppository or transdermal patch.

35. The use of claims 18-34 to treat the symptoms of withdrawal due to cessation of tobacco use.

36. The use of claims 18-34 to treat the symptoms of obesity.

37. The use of claims 18-34 to treat the symptoms of drug and alcohol addiction, heavy metal poisoning, adverse effects of antineoplastic disease treatment, antineoplastic disease and endocrine and immune system disorders.

38. The use of claims 18-34 to treat the symptoms of respiratory disease, disorders of the central and peripheral nervous systems, cardiac insufficiency and circulatory disease and dysfunction of gastrointestinal motility and irritable bowel syndrome, and fatigue syndrome.

INTERNATIONAL SEARCH REPORT

Interr ...al Application No
PCT/CA 98/00094

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/46 //(A61K31/46,31:44)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 925 856 A (HARRIS III RALPH N ET AL) 15 May 1990 cited in the application see column 1, line 38 - line 50 ---	1-38
A	US 4 713 391 A (CHIANG PETER K ET AL) 15 December 1987 cited in the application see column 1, line 32 - line 51 ---	1-38
A,O	US 3 063 901 A (O'LEARY ET AL.) 13 November 1962 cited in the application see claims -----	1-38

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 May 1998	10.06.98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Leherte, C

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

I. ıational application No.
PCT/CA 98/00094

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 18-38 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

In view of the very large number of compounds which are defined by the wording of the claims, the search has been performed on the general idea and the combinations explicitly mentionned in the examples

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

...formation on patent family members

Interna...al Application No
PCT/CA 98/00094

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4925856 A	15-05-1990	NONE	
US 4713391 A	15-12-1987	NONE	
US 3063901 A	13-11-1962	NONE	